PERSPECTIVE

Missed Opportunities in Embryonic Stem-Cell Research

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Three years have passed since August 9, 2001, when President George W. Bush drew a line in the sand: he announced that research on human embryonic stem cells created before that date would be supported by federal dollars; research on lines created later would not. The President's policy has severely curtailed opportunities for U.S. scientists to study the cell lines that have since been established, many of which have unique attributes or represent invaluable models of human disease.

Some 128 new human embryonic stem-cell lines have been produced worldwide since the President's announcement.[1] Douglas Melton et al. of Harvard University published in the *Journal* a thorough description of 17 new lines that can be cultured with less cumbersome techniques than those previously used.[2] In Singapore, Bongso and colleagues have cultured new lines uncontaminated by nonhuman animal products, such as serum or mouse feeder cells, that are therefore preferable for applications in human patients. At the recent meetings of the International Society for Stem Cell Research, a group from the Reproductive Genetics Institute of Chicago described nearly 50 novel lines, at least 10 of them derived from embryos carrying genetic diseases identified through preimplantation diagnosis-including neurofibromatosis type 1, Marfan's syndrome, the fragile X syndrome, myotonic dystrophy, and Fanconi's anemia. Such conditions constitute a minute fraction of the disorders that can be investigated with new embryonic stem cells. Though the federal government is the principal patron of peer-reviewed biomedical research, U.S. scientists studying these cell lines cannot obtain grant support through the National Institutes of Health (NIH); they must find funding from private foundations or philanthropic sources that seldom provide predictable, long-term support.

Many opportunities are being missed, most obviously those pertaining to the diseases listed above. In my laboratory, for example, we are eager to obtain the line carrying the gene defect responsible for Fanconi's anemia. With it, we could investigate how this mutation influences blood development during the differentiation of embryonic stem cells, study the characteristic genetic and chromosomal instability of these cells, test methods for gene repair, and screen for drugs that ameliorate the abnormality. Such investigations would provide new insights into disease pathophysiology and might lead to treatments. But the President's policy prohibits us from using our federal grants to pursue these avenues.

Instead, using the 21 lines currently listed in the NIH registry, U.S. scientists are limited to exploring generic questions about human embryonic stem cells. What are the optimal culturing conditions? What factors promote self-renewal? How do we coax the cells to become blood cells, neurons, or muscle cells? How can one genetically modify the cells? What genes are expressed? Although the pre-2001 lines facilitate these basic studies, they have limited potential for use in clinical therapies. All were cultured in contact with mouse cells and bovine serum, which renders them inferior to newer lines, derived under pristine conditions, for potential therapeutic applications. Moreover, given the limited genetic diversity of the lines, transplantation of their products would face the same immune barrier as organ transplantation. More important questions can be addressed only by means of the lines modeling specific diseases, and therapies may best be pursued with lines genetically matched to specific patients through somatic-cell nuclear transfer. Such approaches are precluded by current policy.

The Presidential challenger Senator John Kerry (D-Mass.) has stated that he would overturn the Bush restrictions and allow federal funding for research involving any human embryonic stem-cell line. Although a boon to stem-cell research, a change of administration would not immediately clear the way for important areas of embryo research. An even more restrictive element of government policy prohibits the use of funds for "the creation of a human embryo or embryos for research

purposes; or . . . research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death." Proposed in 1996 by Representative Jay Dickey (R-Ark.) as a rider on the appropriations bill for the Department of Health and Human Services and renewed every year since, the Dickey Amendment prohibits federal engagement in a field of research pertaining to the nature of the human embryo, its disorders of development, and the derivation of new human embryonic stem-cell lines. Although most embryos created in vitro during fertility procedures are deemed unsuitable for pregnancy and are discarded, federal funds may not be used to ascertain what went wrong. Such studies, beyond improving the efficacy of fertility treatments, offer promise for understanding many chromosomal and developmental disorders that originate in the early embryo.

The Dickey Amendment prohibits federally funded scientists from deriving lines that model human disease. The use of somatic-cell nuclear transfer to generate pluripotent lines from patients with disorders such as schizophrenia, Alzheimer's disease, amyotrophic lateral sclerosis, and diabetes offers new strategies for unraveling the pathophysiology of these conditions, and the derivation of lines from patients with genetic diseases such as sickle cell anemia and immune deficiency hold promise for combining gene therapy with autologous cell-replacement therapy. Such studies have an immediate, compelling medical rationale, yet they cannot be pursued with federal grants.

As research struggles forward in the absence of federal funding, the number of embryonic stem-cell lines will continue to grow, creating ever more valuable tools that are out of reach for U.S. scientists. Biomedical scientists are inherently innovators, drawn to new technologies, and these missed opportunities are difficult to accept. The science of human embryonic stem cells is in its infancy, and the current policies threaten to starve the field at a critical stage. The explosive growth of research that followed the isolation of mouse embryonic stem cells in 1981 ushered in a revolution in developmental biology. It will be discouraging if studies of human embryonic stem cells, which have such profound implications for human health, are unable to keep pace.

Dr. Daley reports that he is a member of the scientific advisory board and board of directors of, and has options to purchase equity in, ViaCell, a company that banks cord blood and investigates the use of cord-blood stem cells. He also reports serving as a medical and scientific advisor to MPM Capital.

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1. Cook G. 94 New cell lines created abroad since Bush decision. Boston Globe. May 23, 2004:A14.
2. Cowan CA, Klimanskaya I, McMahon J, et al. Derivation of embryonic stem-cell lines from human blastocysts. N Engl J Med 2004;350:1353-6.

Sins of Omission — Cancer Research without Informed Consent

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Avir Kagan was an attending physician at Brooklyn's Jewish Chronic Disease Hospital (JCDH) in 1963, when he received a surprising request: Would he participate in an experiment in which live cancer cells were injected into chronically ill patients? Although Kagan said no, some of his colleagues agreed. By 1964, an enormous controversy had erupted, and the hospital's staff was being compared to Nazi physicians who had performed brutal experiments in concentration camps.

How did it happen that 22 patients received injections of cancer cells without their knowledge? On the 40th anniversary of this scandal, what can it teach us about the ethics of human experimentation?

The physician who spearheaded the experiment, Chester M. Southam, was a respected clinical investigator at the Memorial Sloan-Kettering Cancer Center who was studying the immunology of cancer. He had injected cancer cells into hundreds of patients with cancer, generating nodules that grew for several weeks before regressing. In contrast, similar injections in healthy volunteers showed much more rapid rejection.[1] These findings suggested that patients with cancer lacked immunity to their disease, but Southam wanted to make sure that this phenomenon was not attributable solely to their debilitated state. So he sought out chronically ill people who did not have cancer.

Southam approached Emanuel E. Mandel, director of the Department of Medicine at JCDH. Mandel agreed to cooperate, and it was he who asked Kagan